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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/697,526	10/30/2003	Paz Einat	68300-A/JPW/DNS	7662

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EXAMINER

FETTEROLF, BRANDON J

ART UNIT	PAPER NUMBER
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1642

DATE MAILED: 08/24/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

10/697,526

Applicant(s)

EINAT ET AL.

Examiner

Brandon J. Fetterolf, PhD

Art Unit

1642

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 20 June 2005.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-29 is/are pending in the application.
- 4a) Of the above claim(s) 3,4,8,9 and 12-29 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1,2,5-7,10 and 11 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: _____

DETAILED ACTION

Election/Restrictions

The Election filed on June 20, 2005 in response to the Restriction Requirement of March 18, 2005 has been entered. Applicant's election of claims 1-2, 5-7 and 10-11, as specifically drawn to a method of treatment for an apoptosis related disease in a subject comprising administering a siRNA.

Applicant's election of claims 1-2, 5-7 and 10-11 with traverse is acknowledged. The traversal is on the grounds that restriction may be required if two or more independent and distinct inventions are claimed in one application. Applicant's argue that under MPEP 802.01 the inventions are not independent. For example, Applicants contend that the inventions of Groups I-II are both drawn to methods of treating an apoptosis-related disease in a subject by administering an inhibitor of the ATRX polypeptide. Moreover, Applicants assert that under MPEP 803, there are two criteria for a proper restriction requirement: 1) the invention must be independent or distinct (as discussed above) and 2) there must be a serious burden on the Examiner if restriction is required. For instance, Applicants submit that there would not be a serious burden on the Examiner if restriction is not required between Groups I-XIII because a search of the prior art for a method of treatment for an apoptosis-related disease in a subject comprising administering siRNA, would necessarily turn up prior art for the claims of Groups I-XIII. These arguments have been considered, but are not found persuasive.

First, while Applicants contend that under MPEP 802.1 the inventions of Groups I-II are not independent, Applicants are reminded that the MPEP clearly asserts that restriction is proper when invention are independent OR distinct. In the instant case, the inventions were shown to be patentably distinct for the reasons set forth in the prior office action (pages 4-6). As to the question of burden of search, the inventions are classified differently, necessitating different searches of the US Patents. Further, classification of subject matter is merely one indication of the burdensome nature of the search involved. The literature search, particularly relevant in this art, is not coextensive and is much more important in evaluating the burden of search. Different searches and issues are involved in the examination of each group.

Art Unit: 1642

For these reasons the restriction requirement is deemed to be proper and is therefore made FINAL.

Claims 1-29 are currently pending.

Claims 3-4, 8-9 and 12-29 are withdrawn from consideration as being drawn to non-elected inventions.

Claims 1-2, 5-7 and 10-11 are currently under consideration.

Specification

The specification is objected to for improper disclosure of amino acid sequences without a respective sequence identifier, i.e. a SEQ ID NOs.; see for example, Figure 3 and Figure 4. Hence, the disclosure fails to comply with the requirements of 37 CFR 1.821 through 1.825. In the absence of a sequence identifier for each sequence, Applicant must provide a computer readable form (CRF) copy of the sequence listing, an initial or substitute paper copy of the sequence listing, as well as any amendment directing its entry into the specification, and a statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 CFR 1.821(e-f) or 1.825(b) or 1.825(d).

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-2, 5-7 and 10-11 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-2, 5-7 and 10-11 are rejected as vague and indefinite for reciting the term ATRX as the sole means of identifying the claimed molecule. The use of laboratory designations only to identify a particular molecule renders the claims indefinite because different laboratories may use the same laboratory designations to define completely distinct molecules. The rejection can be obviated by amending the claims to specifically and uniquely identify ATRX, for example, by SEQ ID NO. and function of ATRX.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-2, 5-7 and 10-11 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir, 1988). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (Wands, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art; (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

The instant claims read on a method for treatment of an apoptosis-related disease in a subject comprising administering to a subject a therapeutically effective amount of an inhibitor of the ATRX polypeptide in a dosage sufficient to inhibit ATRX so as to treat the subject. Thus, the claims read on an in vivo treatment method including, but not limited to, gene therapy, wherein the ATRX inhibitor is a siRNA.

The instant claims are not commensurate with the enablement of the instant disclosure, because practice of the claimed invention would require undue experimentation by an artisan of ordinary skill in the art. The instant specification is not enabling for claims drawn to a method for

Art Unit: 1642

treatment of an apoptosis-related disease in a subject comprising administering to a subject a therapeutically effective amount of an inhibitor of the ATRX polypeptide in a dosage sufficient to inhibit ATRX so as to treat the subject. The specification teaches (page 13, line 1+) that inhibitors of an ATRX polypeptide, which can be used in the treatment of an apoptosis-related disease, include: an antisense oligonucleotide, a modified ATRX polypeptide, an siRNA, an expression vector, an antibody or a small chemical molecule. The specification further provides (page 36, Example 2 and Figure 4 a-b) an example, wherein cells harboring either of the two ATRX antisense fragments were found to be more sensitive to FAS mediated apoptosis than the control cells. Thus, while the specification clearly teaches the *in vitro* effects for at least ATRX antisense fragments, the specification appears to be silent on the *in-vivo* efficacy of any inhibitor of the ATRX polypeptide including, siRNA. The specification does not show any success in treating an apoptosis-related disease by administering a therapeutically effective amount of an inhibitor of the ATRX polypeptide. The specification does not contain any teachings that address the ability of the composition to treat a human subject or even its ability to work *in vivo*. With regards to siRNA specifically, the specification has not taught an appropriate tested dose for humans, the amount of siRNA expression necessary for successful treatment, the number of cells to be treated, the number of times the treatment needs to be administered or the most appropriate route of administration. Therefore, one cannot extrapolate the teachings of the specification to the scope of the claims because the claims are drawn to a general treatment of an apoptosis-related disease by administering an inhibitor of the ATRX polypeptide and more specifically, the treatment of an apoptosis-related disease by administering an ATRX siRNA.

The instant specification provides insufficient guidance and objective evidence to predictably enable one of skill in the art to use the invention as claimed. Those of skill in the art recognize that *in vitro* assays and or cell-cultured based assays are generally useful to observe basic physiological and cellular phenomenon such as screening the effects of potential drugs. However, clinical correlations are generally lacking. The greatly increased complexity of the *in vivo* environment as compared to the very narrowly defined and controlled conditions of an *in- vitro* assay does not permit a single extrapolation of *in vitro* assays to human diagnostic efficacy with any reasonable degree of predictability. *In vitro* assays cannot easily assess cell-cell interactions that may be important in a particular pathological state. Furthermore it is well known in the art that cultured cells, over a period

Art Unit: 1642

time, lose phenotypic characteristics associated with their normal counterpart cell type. Freshney (Culture of Animal Cells, A Manual of Basic Technique, Alan R. Liss, Inc., 1983, New York, p4) teach that it is recognized in the art that there are many differences between cultured cells and their counterparts *in vivo*. These differences stem from the dissociation of cells from a three-dimensional geometry and their propagation on a two-dimensional substrate. Specific cell interactions characteristic of histology of the tissue are lost. The culture environment lacks the input of the nervous and endocrine systems involved in homeostatic regulation *in vivo*. Without this control, cellular metabolism may be more constant *in vitro* but may not be truly representative of the tissue from which the cells were derived. This has often led to tissue culture being regarded in a rather skeptical light (p. 4, see Major Differences In Vitro). Further, Dermer (Bio/Technology, 1994, 12:320) teaches that, petri dish cancer" is a poor representation of malignancy, with characteristics profoundly different from the human disease. Dermer teaches that when a normal or malignant body cell adapts to immortal life in culture, it takes an evolutionary type step that enables the new line to thrive in its artificial environment. This step transforms a cell from one that is stable and differentiated to one that is not. Yet normal or malignant cells *in vivo* are not like that. The reference states that evidence of the contradictions between life on the bottom of a lab dish and in the body has been in the scientific literature for more than 30 years. Clearly it is well known in the art that cells in culture exhibit characteristics different from those *in vivo* and cannot duplicate the complex conditions of the *in vivo* environment involved in host-tumor and cell-cell interactions.

Moreover, if the method of treatment of an apoptosis-related disease was by gene therapy, those of skill in the art would recognize the unpredictability of treating a disease by a method of gene therapy. Gene therapy using administration of recombinant nucleic acids involving *in vivo* or *ex vivo* methods had not seen any success despite a great deal of work and resources. Several reviews in the art show that difficulties with vector selection, mode of delivery and persistence of predictable and effective levels of expression of the protein, created technical barriers to the practice of gene therapy methods. Verma et al states that, "[t]he Achilles heel of gene therapy is gene delivery...", and that, "most of the approaches suffer from poor efficiency of delivery and transient expression of the gene" (Verma et al. (1997) Nature Volume 389, page 239, column 3, paragraph 2). Marshall concurs, stating that, "difficulties in getting genes transferred efficiently to target cells- and getting them expressed-remain a nagging problem for the entire field", and that "many problems must be

solved before gene therapy will be useful for more than the rare application” (Marshall (1995) Science, Volume 269, page 1054, column 3, paragraph 2, and page 1055, column 1).

Numerous factors complicate the gene therapy art which have not been shown to be overcome by routine experimentation. Eck et al. (Goodman & Gilman's The Pharmacological Basis of Therapeutics (1996), 9th Edition, Chapter 5, McGraw-Hill, NY) explains, “the delivery of exogenous DNA and its processing by target cells requires the introduction of new pharmacokinetic paradigms beyond those that describe the conventional medicines in use today”. Eck et al teaches that with *in vivo* gene transfer, one must account for the fate of the DNA vector itself (volume of distribution, rate of clearance into the tissues, etc.), the *in vivo* consequences of altered gene expression and protein function, the fraction taken up by the target cell population, the trafficking of the genetic material within cellular organelles, the rate of degradation of the DNA, the level of mRNA produced, the stability of the mRNA produced, the amount and stability of the protein produced, and the protein's compartmentalization within the cell or its secretory fat, once produced. These factors differ dramatically based on the vector used, the protein being produced and the disease being treated (see Eck et al, bridging pages 81-82).

Also among the many factors that the art teaches affect efficient gene delivery and sustained gene expression are, immune responses and the identity of the promoter used to drive gene expression. Verma et al teaches, in reference to *ex vivo* methods, that weak promoters produce only low levels of therapeutically effective protein, and that only by using appropriate enhancer-promoter combinations can sustained levels of therapeutically effective protein be achieved (Verma et al, *supra*, page 240, column 2). Verma et al further warns that, “...the search for such combinations is a case of trial error for a given cell type” (Verma et al, *supra*, page 240, bridging sentence of columns 2-3). The state of the art is such that no correlation exists between successful expression of a gene and a therapeutic result (Ross et al, Human Gene Therapy, 1996, Volume 7, pages 1781-1790, see page 1789, column 1, first paragraph). Thus, the art at the time at the time of filing clearly establishes that expectation for achieving a desired therapeutic effect *in vivo* by expressing a therapeutic gene using any of the expression constructs known in the art was extremely low.

More recently, Rubanyi (Mol. Aspects Med. (2001) 22:113-142) teaches that the problems described above remain unresolved. Rubanyi states, “[a]lthough theoretical advantages of [human gene therapy] are undisputable, so far [human gene therapy] has not delivered the promised results:

Art Unit: 1642

convincing clinical efficacy could not be demonstrated yet in most of the trials conducted so far...” (page 113, paragraph 1). Among the technical hurdles that Rubanyi teaches remain to be overcome are problems with gene delivery vectors and improvement in gene expression control systems (see “3. Technical hurdles to be overcome in the future”, beginning on page 116 and continued through page 125). Furthermore, Juengst (British Medical Journal (2003) Volume 326, pages 1410-1411) teaches the unpredictable nature of gene therapy and that a few of the apparent successes actually developed T cell-acute lymphoblastic leukemia due to insertional mutagenesis at or near the LMO-2 gene causing altered gene expression. The art has demonstrated that a large amount of experimentation has already been performed without demonstrating successful gene therapy methods for treatment of disease.

Thus, in order to practice the claimed invention, the skilled artisan would not have found sufficient guidance in the specification to achieve effective levels of the expressed nucleic acid, to select a proper dose or administration route or to determine other factors for a successful treatment. The prior art did not compensate for the lack of guidance in the specification since the teachings do not recognize any clearly successful gene therapy methods. The skilled artisan would have had to engage in a large amount of experimentation to practice the claimed invention. In view of the lack of guidance and the large amount of experimentation in an unpredictable art, it would require undue experimentation to practice the claimed invention.

Therefore, NO claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brandon J. Fetterolf, PhD whose telephone number is (571)-272-2919. The examiner can normally be reached on Monday through Friday from 8:30 to 5:00.


If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeff Siew can be reached on 571-272-0787. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Art Unit: 1642

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Brandon J Fetterolf, PhD
Examiner
Art Unit 1642

BF


JEFFREY SIEW
SUPERVISORY PATENT EXAMINER
6/19/05